Subclinical Inflammation and Simple Blood Parameters in Pregnant with Familial Mediterranean Fever

Ailesel Akdeniz Ateşi Olan Gebelerde Basit Kan Parametreleri ve Subklinik İnflamasyon Arasındaki İlişki

Inflammation in Familial Mediterranean Fever

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Özet

Amaç: Ailesel Akdeniz Ateşi (AAA), herediter monogenik otoinflamatuar hastalıklardan en sık görülenidir. AAA hastalarında yapılan çalışmalar, inflamasyonun ataksız dönemlerde dahi devam ettiğini göstermektedir. Bu çalışmada, AAA olan gebe grubunda, semptomsuz dönem boyunca kronik inflamasyonu belirlemek için ortaya çıkmış inflamatuar belirteçler olarak nötrofil lenfosit oranı (NLO), platelet lenfosit oranı (PLO), lenfosit monosit oranı(LMO), ortalama trombosit hacmi (MPV), platelet dağılım aralığı(PDW) gibi basit kan parametrelerinin potansiyelinin değerlendirilmesi amaçlanmıştır. Gereç ve Yöntem: Çalışmaya 33 tanesi AAA olan ve 32 tanesi sağlıklı gebelerden oluşan toplamda 65 tekil gebelik dahil edildi. Bu gebeler birinci trimesterden gebeliğin sonuna kadar takip edildi. Gebelerden biyokimyasal analizler (C-reaktif protein, fibrinojen) için kan örnekleri alındı. 11-13 hafta taraması ve 16-19 haftalarda detaylı inceleme sonrası tam kan sayımı elde edildi. Bulgular: Her iki grup arasında ortalama NLO, PLO, PDW, LMO ve fibrinojen değerleri benzer olmasına rağmen, birinci ve ikinci trimesterde kontrol grubu ile kıyaslandığında AAA olan gebelerde ortalama yüksek duyarlı CRP değerleri anlamalı derecede yüksek ve MPV değerleri anlamlı derecede düşük çıkmıştır. İkinci trimesterde yüksek duyarlı CRP düzeyleri ile MPV arasında negatif korelasyon bulunmaktadır (r= -0.375 p=0.003). Tartışma: AAA olan gebelerimizin hepsi başvuru anında düzenli olarak kolşisin kullandığından dolayı en azından teorik olarak kolşisinin trombositler üzerindeki anti-inflamatuar ve potansiyel etkilerinden dolayı bu tedavi sonuçlarımızı değiştirmiş olabilir. Ayrıca MPV, AAA olan gebelerde negatif akut faz reaktanı olarak kullanılabilir.

Anahtar Kelimeler

İnflamasyon; Lenfosit Monosit Oranı; Nötrofil Lenfosit Oranı; Gebelik; Trombosit

Abstract

Aim: Familial Mediterranean Fever (FMF) is the most common hereditary monogenic auto-inflammatory disease. Studies suggest that inflammation persists even in attack-free periods in FMF patients. In this study, we aim to investigate the potential of simple blood parameters including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), mean platelet volume (MPV), and platelet distributed width (PDW) as emerging inflammatory markers to identify chronic inflammations during symptom-free periods in a group of pregnant patients with FMF. Material and Method: A total of consecutive 65 singleton pregnancies, 33 with FMF and the other 32 healthy women, were followed from the first trimester to the end of the pregnancies. Blood samples for biochemical analyses (C-reactive protein, fibrinogen) and a complete blood count were obtained at 11-13 weeks and at 16-19 weeks following a detailed examination. Results: While the mean, NLR, PLR, PDW, fibrinogen, and LMR values were comparable between the groups, the mean hs-CRP levels were significantly higher and MPV values were significantly lower in the FMF group compared with the control group at both the first and second trimester. There was a significant negative correlation between hs-CRP levels with MPV at second trimester (r= -0.375 p=0.003). Discussion: Since all of our FMF patients had already been on regular colchicine therapy on admission, we admit, at least theoretically, that the anti-inflammatory and potential effects of colchicine on platelets could have altered our results. Otherwise, MPV may be used as a negative acute-phase reactant in pregnant patients with FMF.

Keywords

Inflammation; Lymphocyte To Monocyte Ratio; Neutrophil To Lymphocyte Ratio; Pregnancy; Platelet

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Introduction

Familial Mediterranean Fever (FMF) is the most common hereditary monogenic auto-inflammatory disease, characterized by recurrent, self-limited episodes of fever and sterile inflammation of serous membranes. FMF is caused by mutations in the Mediterranean fever gene that encodes pyrin (also known as Marenostrin), which is essentially responsible for the regulation of apoptosis, cytokines, and inflammation [1].

The diagnosis of FMF is still based on clinical criteria since there is no specific diagnostic test. Tel Hashomer criteria are widely used for diagnosis of FMF [2].

The treatment of patients with FMF is aimed at suppressing the inflammation. Colchicine, an anti-inflammatory drug, is the first-line therapy to treat pain and to prevent amyloidosis in FMF; it can be used safely in pregnancy [3].

Studies suggest that inflammation persists even in attack-free, asymptomatic periods in FMF patients as shown by high levels of acute-phase proteins, cytokines, and inflammation-induced proteins [4].

Systemic inflammation can be measured by using a variety of biochemical and hematological markers. Recent findings indicate that measuring blood cell subtype ratios, such as the neutrophil to lymphocyte ratio (NLR), the platelet to lymphocyte ratio (PLR), and the lymphocyte/monocyte ratio (LMR), might provide prognostic and diagnostic clues to diseases related to chronic low-grade inflammation [5, 6]. Mean platelet volume (MPV) and platelet distributed width (PDW) are other examples of noninvasive biomarkers that can be easily tested [7,8].

In this study, we aim to investigate the potential of simple blood parameters including NLR, PLR, LMR, PDW, and MPV as emerging inflammatory markers to identify chronic inflammations during symptom-free periods in a group of pregnant patients with FMF. We also aim to investigate whether pregnant patients with FMF have an increased risk for perinatal complications.

Material and Method

This prospective case–control study was conducted between December 2014 and August 2015. Local Institutional Review Board approved the study and the universal principles of the Helsinki Declaration were applied. All patients provided written informed consent.

The diagnosis of FMF was made according to the Tel Hashomer criteria. The definitive diagnosis of FMF was made when two major criteria or one major and two minor criteria were present. The major criteria are: 1- recurrent febrile episodes accompanied by serositis, 2- AA type amyloidosis without apparent predisposing disease, and 3- favorable response to colchicine test. Minor criteria are: 1- recurrent febrile episodes, 2- erysipelas-like skin lesions, and 3- diagnosis of FMF in a first-degree relative [2].

All of the patients had Turkish ethnicity determined by country of origin. Of these, the women with FMF were already on colchicine treatment in appropriate doses to prevent attacks (1-2 mg daily). Proteinuria, suggestive of renal amyloidosis, was excluded on the basis of repetitive urine testing. Patients with any of the following criteria were not eligible to participate in the study: multiple pregnancy, detection of fetal anomalies by USG, and the history of any other systemic diseases.

The pregnancies of sixty patients diagnosed with FMF were followed during the study period at our hospital. A total of 27 patients with FMF were excluded from the study:2 had concomitant connective tissue diseases, 1 had diabetes mellitus, 2 had multiple pregnancies, 2 had IVF pregnancy, and 20 were late (after 14th weeks of gestation) registration (Figure 1). Two of the patients were later excluded from the study due to noncompliance and missing data.

A total of 65 consecutive singleton pregnancies who conceived spontaneously, 33 with FMF and 32 healthy women, were followed from the first trimester to the end of the pregnancies.

All of the patients were examined for infection, routine urine cultures were obtained, and body temperatures were measured. Patient with any signs and symptoms of active infection, (pain, fever, or vaginal discharge), were excluded from the study. None of the patients or controls had a multiple pregnancy, active labor, or pre-existing chronic systemic disease.

The diagnosis of preeclampsia was based on a systolic blood pressure of ≥140 mmHg or diastolic blood pressure ≥90 mmHg, measured twice in four-hour intervals while resting, after the 20th gestational week, as well as 300 mg/dL proteinuria detected in a 24-hour urine sample [9]. Preterm birth was defined as delivery before 37 weeks of pregnancy were completed. The diagnosis of fetal growth restriction was made when estimated fetal weight was below the tenth percentile and was associated with abnormal fetal Doppler parameters, with low birth weight defined as <2500 gram and very low birth weight as <1500 gram [10].

Blood samples for biochemical analyses (high-sensitivity C-reactive protein (hs-CRP), fibrinogen) and a complete blood count (CBC) were obtained at 11-13 weeks and at 16-19 weeks after detailed examination.

All CBC analyses were conducted in the central hematology laboratory of the hospital using a Gen-S automated analyzer (Beckman Coulter, High Wycombe, UK). NLR and PLR values were calculated by dividing the absolute neutrophil and platelet counts, respectively, by the absolute lymphocyte counts. LMR value was calculated by dividing the absolute lymphocyte by the absolute monocyte count. Blood samples were taken in standardized, EDTA containing tubes. Measurements were completed within one hour of blood sampling in order to avoid the EDTA-induced platelet swelling with time. Plasma concentrations of hs-CRP were determined with a Tinaquant CRP (Latex) high-sensitive particle-enhanced immuno turbidimetric assay on a Roche Modular P analyzer (Roche kit; Roche Diagnostics) according to manufacturer instructions. Minimum detectable concentration of hs-CRP was 1x10−5 mg/L. All samples were assessed in duplicate.

Maternal characteristics and levels of each participant, such as age, parity, body mass index (BMI), hs-CRP, fibrinogen, and CBC results, were recorded at first and second trimester. The perinatal outcome parameters, including gestational age at delivery, mean birth weight, mode of delivery, preterm delivery, preeclampsia, fetal loss, 5-minute Apgar score, and neonatal intensive care unit admission, were also assessed.

The statistical analyses were performed using IBM SPSS Statistics version 15 (IBM Corp., Armonk, NY). Normal distribution of data was assessed using the Kolmogorov–Smirnov test.

Continuous and normally distributed variables were presented as mean ± standard deviation (SD) and intragroup differences were investigated using one-way analysis of variance. The data were summarized as mean ± standard deviation and median (minimum–maximum). Continuous variables were examined using Kruskal–Wallis tests if the data were not normally distributed. Categorical variables were expressed as number (percentage). Proportions were compared with Fisher's exact test or the chi-square test where appropriate. Pearson's correlation analysis was used to study the correlations between measurements. A two-sided p value <0.05 was considered statistically significant.

Results

Of the 60 patients diagnosed with FMF who were followed during the study period, 33 (55%) were enrolled in the study. The demographic characteristics of the groups are presented in Table 1. Maternal age, parity, and BMI were comparable between the groups. The duration of FMF during pregnancy was 7.1 ± 2.5 years in the study group and all of them were under treatment with colchicine 1.5-2 g daily.

Table 1. Comparison of maternal characteristics of FMF and control group.

	FMF (n=33)	Control (n=32)	p value
Maternal age, years	25± 4.63	28.5± 7.2	0.54
Parity (range)	0 (0-3)	1 (0-2)	0.49
Pre-pregnancy BMI, kg/m2	22.78± 2.6	21.10± 3.1	0.53
Maternal weight gain during pregnancy, kg	12.4± 3	11.7± 4.2	0.74
Smoking	1 (3%)	1 (3,1%)	1
Duration of disease, years	7.1± 2.5	-	-

Data expressed as number (%), mean ± SD, median (minimum - maximum). BMI, Body mass index.

Some inflammation related markers (obtained when all participants were asymptomatic) in both the FMF and control groups are shown in Table 2. While the mean WBC, NLR, PLR, PDW, fibrinogen, and LMR values were comparable between the groups, the mean hs-CRP levels were significantly higher and MPV values were significantly lower in the FMF group when compared with the control group at both the first and second trimesters.

There were no significant differences in mode of delivery (p=0.65). No differences in preterm delivery (p=0.73), preeclampsia (p=1), low Apgar scores (p=1), and NICU admission (p=1) were found between the groups. There were no cases of fetal chromosomal anomaly or perinatal mortality in either of the groups. The comparison of the perinatal outcomes of the FMF and control groups is presented in Table 3.

In correlation analysis, there was a significant negative correlation between hs-CRP levels with MPV at second trimester (r= -0.375 p=0.003).

Discussion

The main observation of this study is the identification of the potential role of novel inflammatory markers including NLR, PLR, LMR, and MPV. We found significantly higher serum hs-CRP and lower MPV levels in patients with FMF during the asymptomatic and attack-free period when compared to the controls at both first and second trimester. Indeed, in this study, we showed a negative correlation between MPV and m-CRP.

Table 2. Inflammation related markers in symptom-free FMF patient and control group.

	FMF Group (n=33)	Control Group (n=32)	p value
Mean Assessment week at 1st trimester	11.5 (11.4-13.4)	12 (11.4-13.5)	0.36
Assessment week at 2nd trimester	17.5 (16-18.5)	18 (17-18.5)	0.63
hs-CRP (mg/ L)			
1st trimester	8.40± 5.1	6.04± 3.5	0.05
2nd trimester	11± 4.6	7.01± 2.1	<0.001
Fibrinogen (gr/L)			
1st trimester	465± 93	433± 105	0.24
2nd trimester	477± 101	461± 92	0.66
WBC count (x103/mm3)			
1st trimester	9.9± 2.5	8.33± 2.03	0.11
2nd trimester	10.1± 2.96	9.33± 2.46	0.64
MPV			
1st trimester	9.50+1.43	10.27+0.98	0.02
2nd trimester	9.02+1.09	10.24+0.93	<0.001
PDW			
1st trimester	12.8± 1.27	11.7± 1.93	0.09
2nd trimester	13.2± 1.34	12.7± 2.21	0.08
NLR			
1st trimester	3.60 (1.70-7.06)	3.25 (1.90-7.22)	0.23
2nd trimester	4.30 (2-9.55)	3.54 (1.97-8.93)	0.19
PLR			
1st trimester	136956.5 (80000-513333.3)	131870 (64319.25-210884.4)	0.53
2nd trimester	133548.4 (50232.56-241818.2)	122334 (77456.65-2007143)	0.47
LMR			
1st trimester	3.80±1.80	3.86±1.38	0.88
2nd trimester	3.66±1.44	3.24±1.18	0.22

Data expressed as number (%), mean ± SD, median (minimum -maximum). hs-CRP, high-sensitivity C-reactive protein; LMR, lymphocyte to monocyte ratio; MPV, mean platelet volume; NLR, Neutrophil/lymphocyte ratio; Platelet; PLR, Platelet/ lymphocyte ratio; PDW; platelet distribution width; WBC, white blood cell.

Table 3. Pregnancy outcomes in patients with FMF and healthy pregnant.

	FMF (n= 33)	Control (n= 32)	p value
Gestational age at delivery, weeks ± SD	39.1±1. 6	39.4± 0.8	0.81
Mean Birth weight, gram ± SD	3220.4± 308	3165.0± 219	0.77
Mode of Delivery	0.65		
Vaginal	21 (63%)	21 (65%)	
C/S	12(37%)	11 (35%)	
Perinatal complications			
Preterm Delivery	7 (21%)	7 (21.8%)	0.73
Preeclampsia	0	1 (3,1%)	1.0
Birth weight <10th percentile	1 (3%)	1 (3,1%)	1.0
5 minute Apgar ≤7	3 (9%)	4(12,5%)	1.0
NICU admission	4 (12%)	3 (9,3)	1.0
Perinatal mortality	-	-	-

Data expressed as number (%), mean ± SD, median (minimum - maximum). NICU, Neonatal intensive care unit.

The attacks of FMF that are caused by neutrophil activation are typically accompanied by leukocytosis and elevation of CRP, fibrinogen, and other inflammatory parameters [4]. Colchicine is one of the oldest known drugs used for prophylaxis of FMF attacks and the prevention of the development of amyloidosis. Its anti-inflammatory mechanism differs from the other anti-inflammatory agents like nonsteroidal anti-inflammatory drugs and glucocorticoids. Instead of being involved in the arachidonic acid pathway, colchicine promotes microtubule depolymerization leading to cytoskeletal changes through cell mitosis, exocytosis, and neutrophil motility. Colchicine not only inhibits neutrophil chemotaxis and the production of interleukin-1, but also down-regulates the tumor necrosis factor alpha-receptors [1-3]. Moreover it has been shown that subclinical inflammation characterized by overproduction of hs-CRP and the other acute-phase reactants persists during remission period in FMF patients. Growing data suggests that colchicine decreases the levels of subclinical inflammation markers in FMF [4]. Indeed previous studies suggested that colchicine use suppresses platelet activation [11,12].

MPV, that universally available routine blood count by automated hemogram, is suggested as an indicator of platelet activation and reactivity that have also been associated with inflammation. Compared to lower platelets, higher platelets have larger granules; they aggregate more rapidly with collagen and increased thromboxane A2synthesis, and they show increased expression of P-selectin, glycoprotein IIb/IIIa and fibrinogen receptors [7].

In previous studies, the MPV levels were measured in patients with FMF. There were contradictory results in the literature. Coban et al. showed significantly higher MPV levels in attack-free periods of FMF patients when compared the healthy participants. They also found a negative correlation between MPV levels and the duration of colchicine treatment, and a positive correlation with delay of diagnosis. They suggested that patients with FMF tend to have increased platelet activation. Therefore, MPV level has been suggested as an index of the comprehensive inflammatory status of the body [13]. However Abanonu et al. reported no statistically significant difference between the FMF patients and the control groups in terms of MPV. They hypothesized that this result may be an effect of the colchicine on platelet function [14]. In another well-designated study, Sahin et al. reported decreased values of MPV in FMF patients during attack and attack-free periods than in healthy subjects [15]. This finding supported our study. We showed lower MPV levels in pregnant patients with FMF during attack-free periods compared to the healthy patients. Since all of our FMF patients had already been on regular colchicine therapy on admission, we admit, at least theoretically, that the anti-inflammatory and potential effects of colchicine on platelets could have altered our results.

Although the cause is not clear, some studies in the literature have shown that the prevalence of preterm births is higher in FMF [16,17]. It has been suggested that FMF is an independent risk factor for preterm delivery [16]. But others reported favorable pregnancy outcomes in patients with FMF treated with colchicine before and after pregnancy [18].

It is difficult to determine an actual cause because preterm birth is a multifactorial pregnancy complication. It has been difficult to determine the risk factors involved in a preterm birth due to various triggers that lead to spontaneous or indicated preterm birth such as idiopathic preterm labor, PPROM, and medical or care-related indications and complications having different etiologies but similar manifestations; these may include severe preeclampsia, placental abruption, and chorioamnionitis [19].

In our current study we documented pregnancy outcomes of pregnant patients with FMF. We showed that their perinatal results were comparable with healthy pregnant women. In this cohort, all participants with FMF continued their colchicine treatment during pregnancy from first trimester safely, and no significant differences were noted regarding congenital malformations.

The strengths of our study are the homogeneity of the characteristics of the women in the study groups and its prospective design. All of the participants were examined for infection and body temperatures were measured before obtaining blood samples. Patients with any signs and symptoms of active infection (pain, fever, or vaginal discharge) were excluded from the study. Moreover, in the present study, since the BMI, the maternal age, and the ethnicity were comparable between the groups, possible confounding effects were also eliminated.

In conclusion, the main findings of our study were that serum hs-CRP levels were still higher and MPV values were lower in pregnant patients with FMF who had already been put on colchicine treatment during the asymptomatic period. On the basis of this observation, it is hypothesized that MPV not only indicates platelet function and activation but also is inversely associated with systemic inflammation. Furthermore, perinatal outcome of patients with FMF was comparable to the patients without FMF.

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Competing interests

The authors declare that they have no competing interests.

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